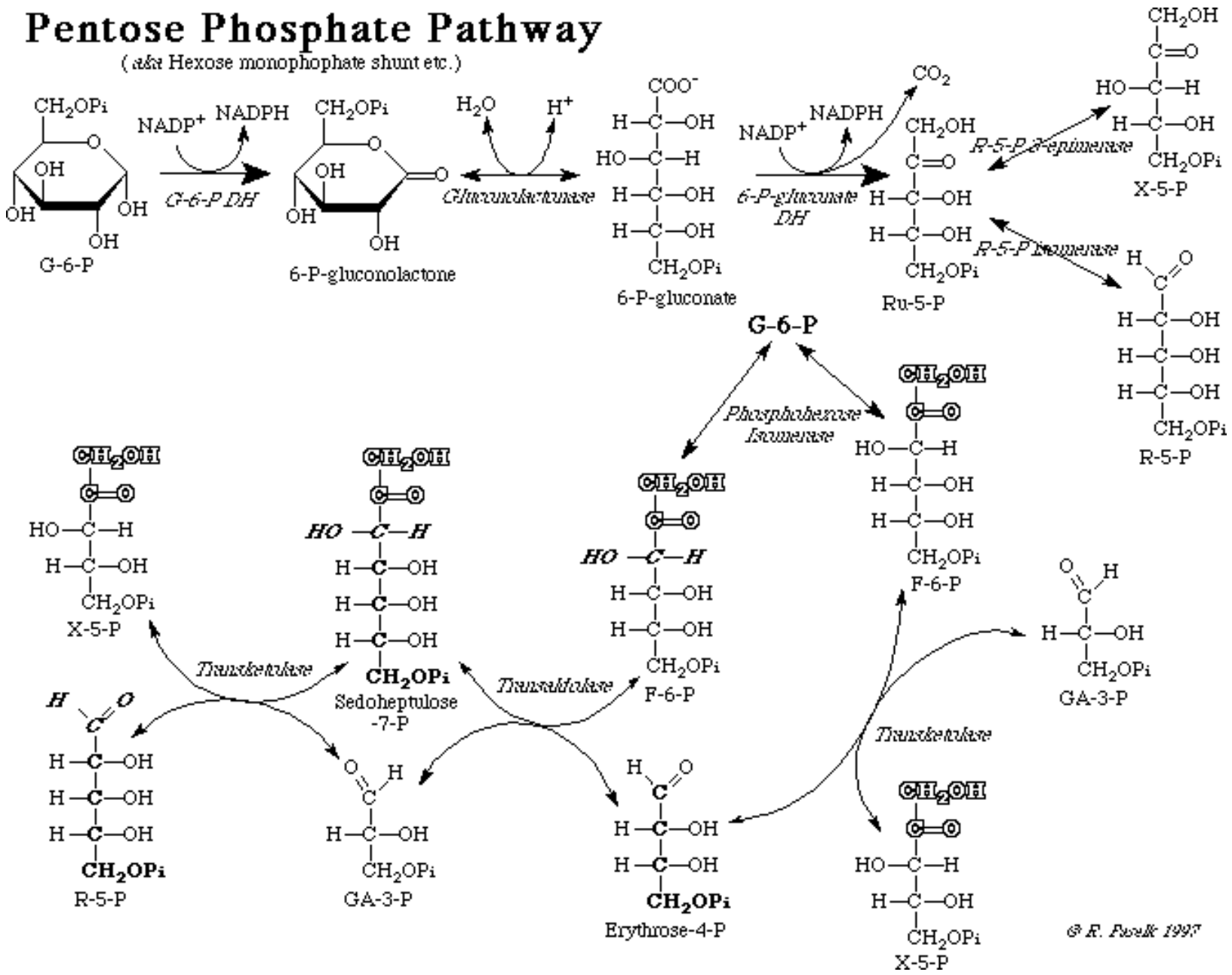
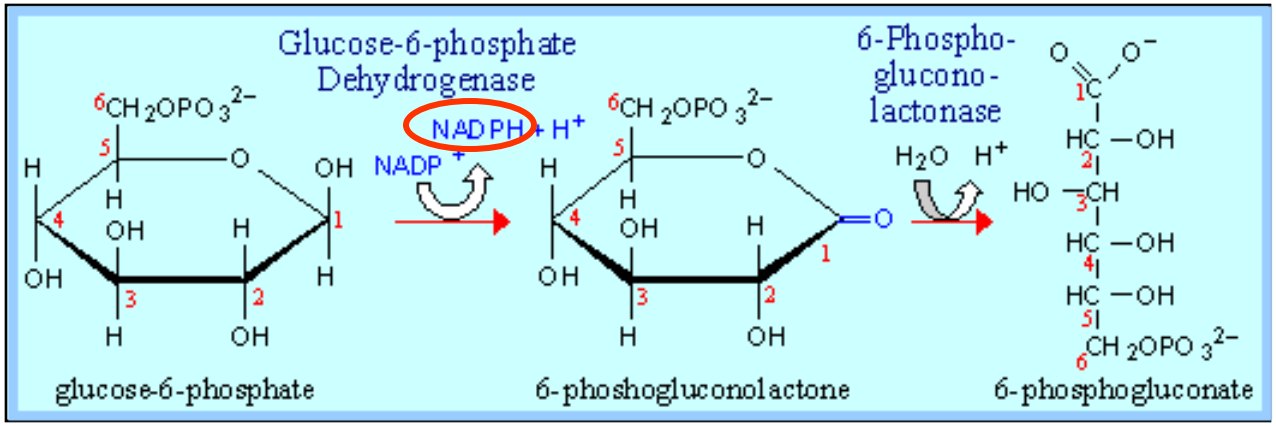
The direct oxidation of glucose: Pentose-phosphate pathway

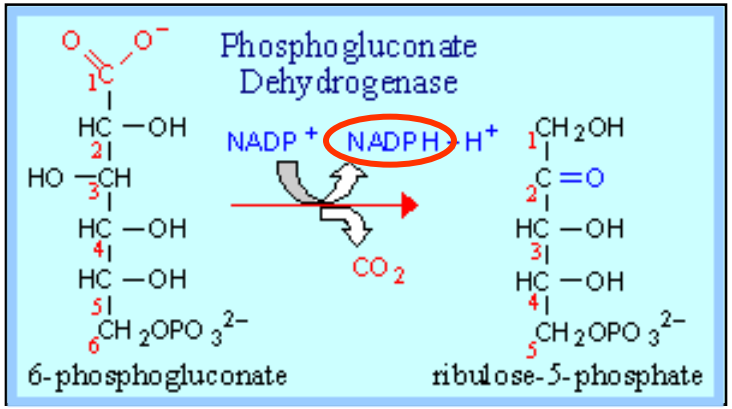


The oxidative first phase of the pentose phosphate pathway

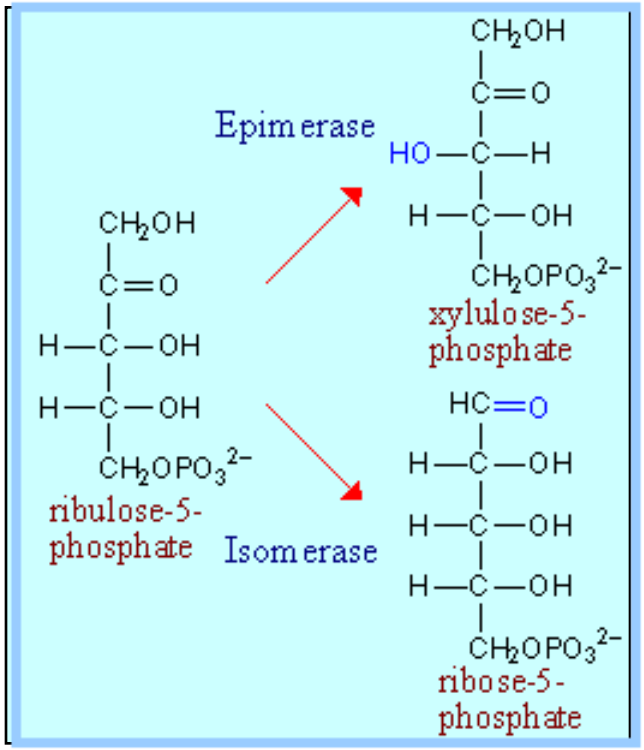


glucose-6-phosphate ⟶ 6-phosphoglucono-δ-lactone

Irreversibile, the committed step of pentose phosphate pathway.



oxidative decarboxylation



D-ribose-5-phosphate: the precursor of nucleotide biosynthesis

Oxidative stage:

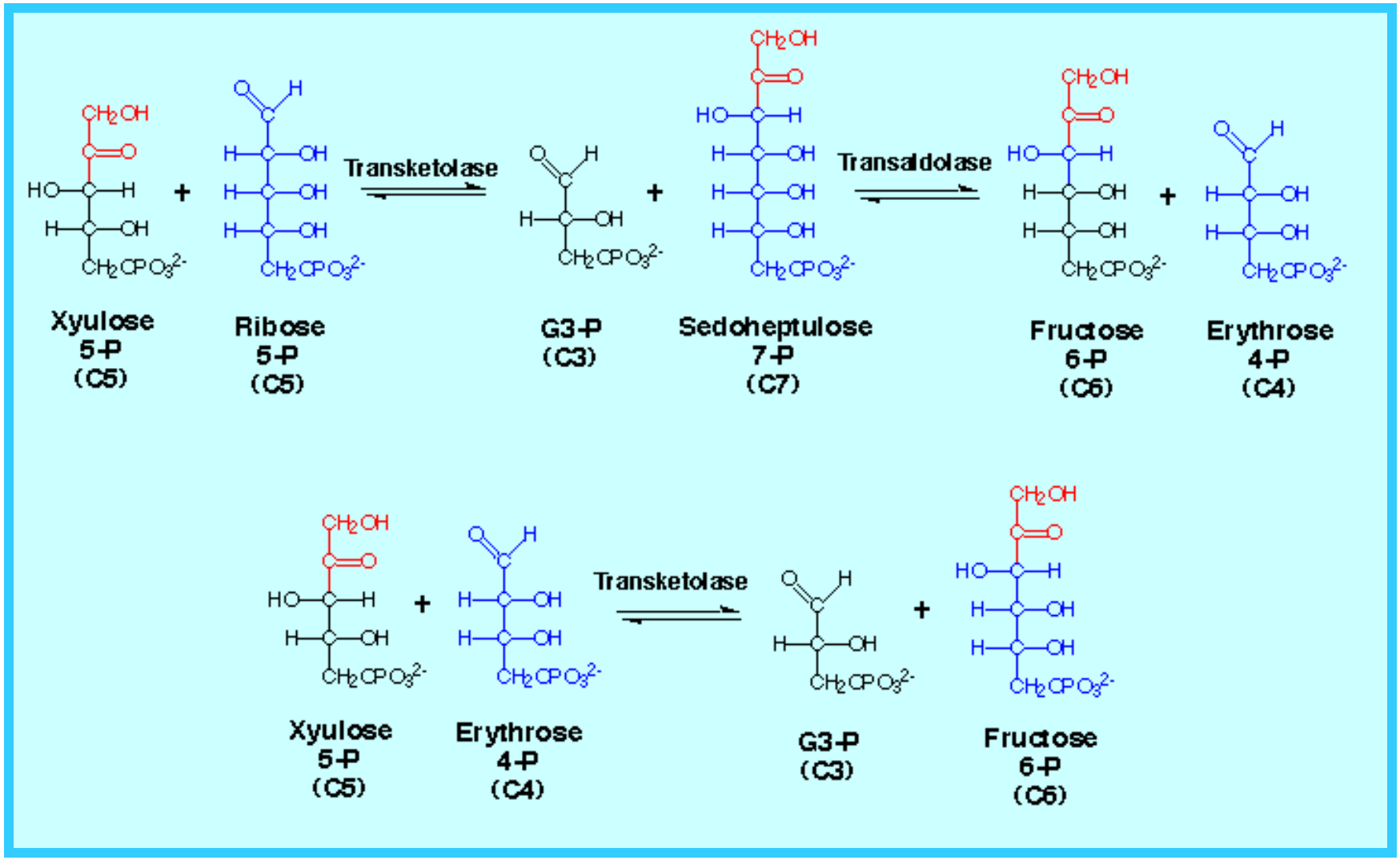
glucose-6-phosphate + H_2O + 2 NAD → ribose-5-phosphate + 2 NADPH + $2H^+$ + CO_2

The nonoxidative phase of the pentose phosphate pathway

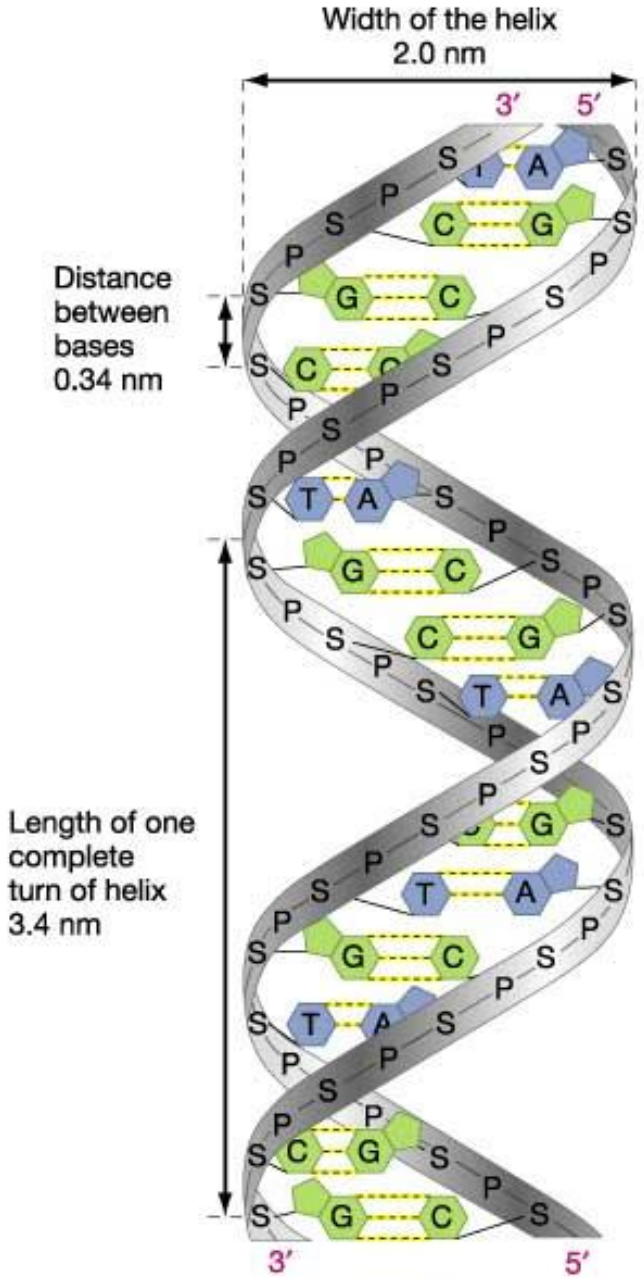
The enzymes involved are:

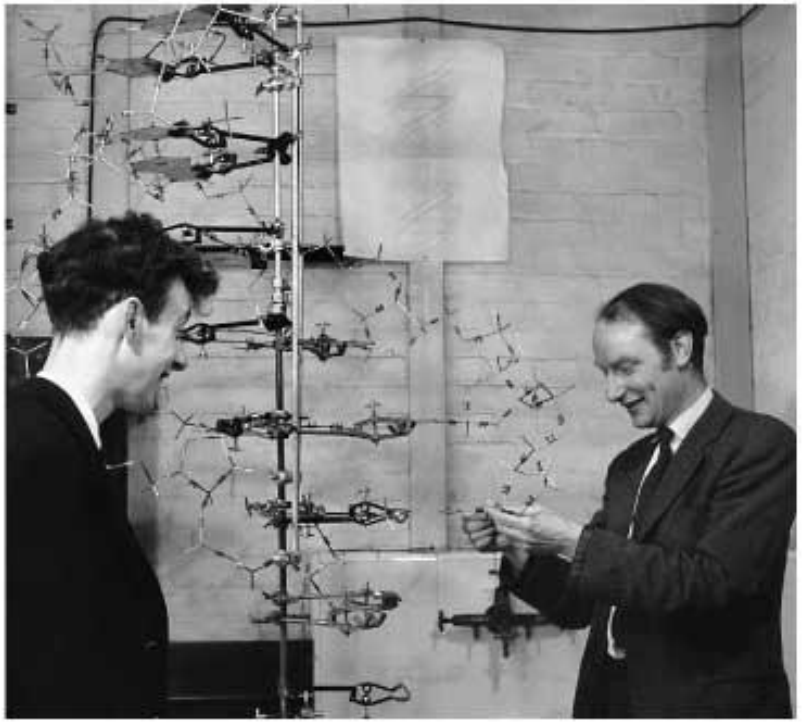
- **an epimerase**
- **an isomerase**
- **Transketolase:** transfers 2-carbon fragments of keto sugars
- **Transaldolase:** transfers a 3-carbon keto fragment

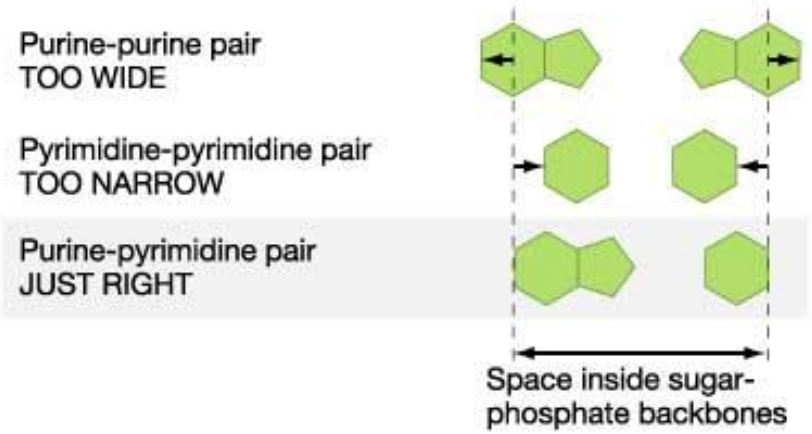
The nonoxidative phase of the pentose phosphate pathway



All the reactions are reversible


Width of the helix
2.0 nm
3′
5′
Distance between bases 0.34 nm
Length of one complete turn of helix 3.4 nm
3′
5′




Purine-purine pair
TOO WIDE
Pyrimidine-pyrimidine pair
TOO NARROW
Purine-pyrimidine pair
JUST RIGHT
Space inside sugar-phosphate backbones

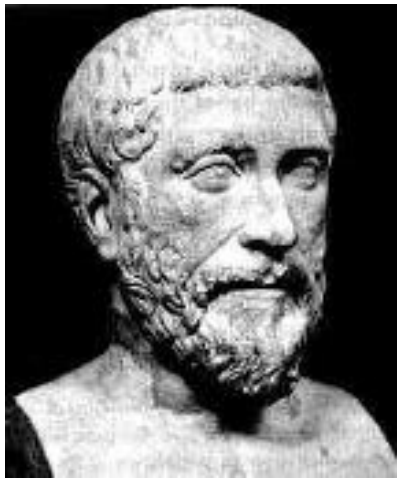
Three different goals three different patways

1. If the cell has produced ribose-5-P, but does not need to synthesize nucleotides, then the ribose-5-P will be converted to glycolytic intermediates

2. If the cell still requires NADPH, the ribose-5-P will be converted back into glucose-6-P using nonoxidative reactions.

3. If the cell already has a high level of NADPH, but needs to produce nucleotides, the oxidative reactions of the pentose phosphate pathway will be inhibited, and the glycolytic intermediates fructose-6-P and glyceraldehyde-3-P will be used to produce the five carbon sugars using exclusively the nonoxidative phase of the pentose phosphate pathway.

Why did not eat Phythagoras falafel?



Vicia Faba: or fava bean a component of falafel

The observation of Phytagoras: the bean make many people sick. He prohibited his follwersfrom dining fava beans

Symptoms: erythrocytes begin to lyse 24-48 hoursafter ingestion of beans, jaundice, kidney failure

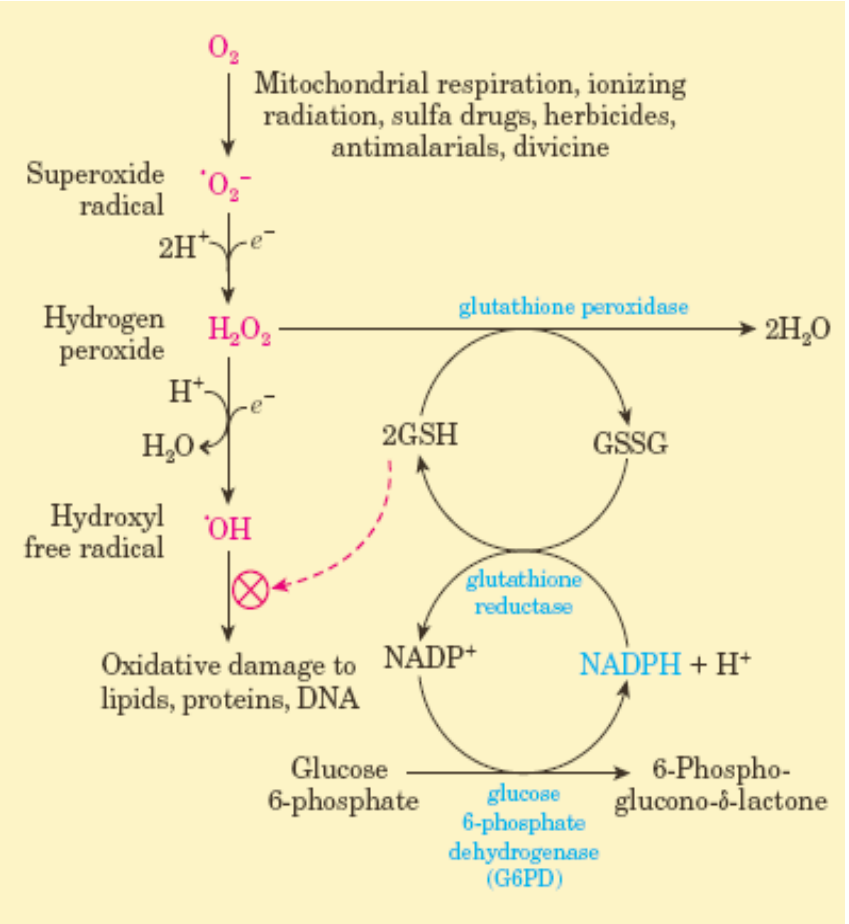
Similar symptomes are caused by primaquine (an natimalarial drug), sulfa antibiotics, herbicides

Background: deficiency of glucose-6-phosphate dehydrogenase Approx. 400 million people are affected. It is a congenital failure, There is no symptomes in general. The symptomes manifest due to the ingestion of certain drugs, foodstuff.

Glükóz-6-foszfát dehidrogenáz: NADPH forrás

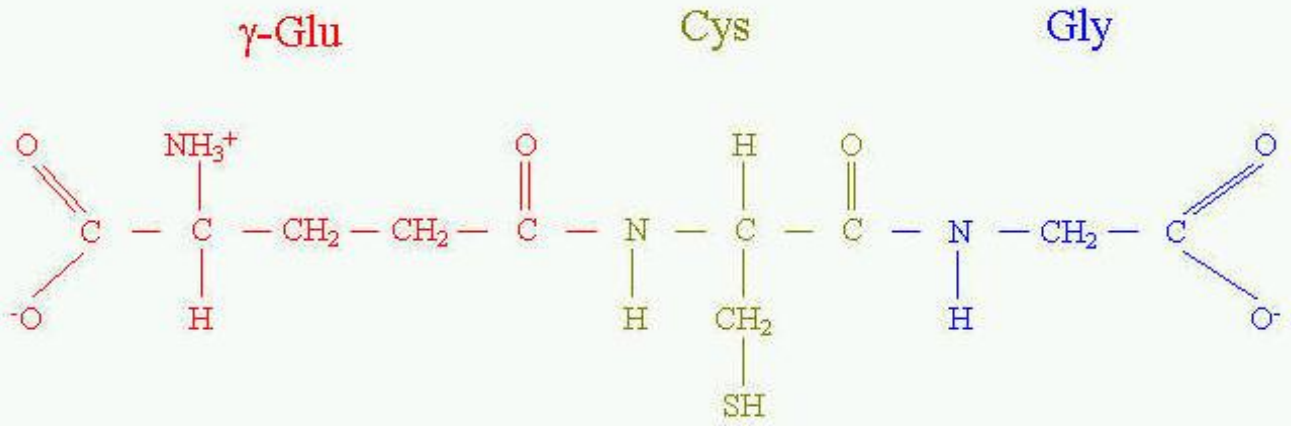
NADPH consumption: biosynthesis, protection from ROS

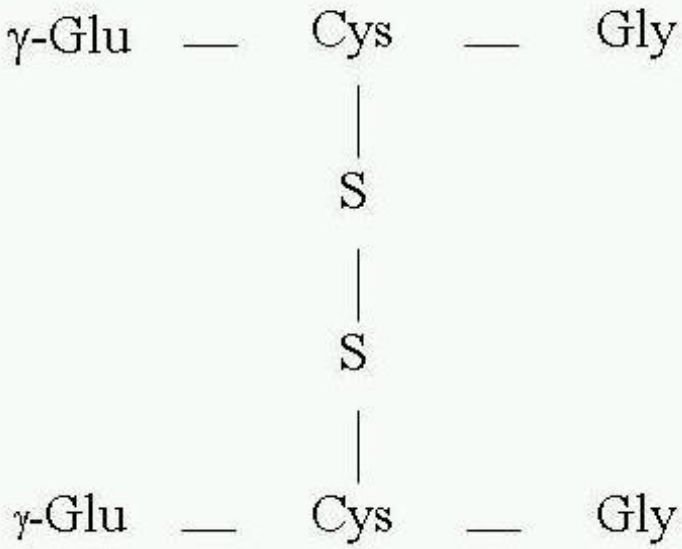
Geographical incidence: The 25% of people are affected in the tropical part of Africa, Middle East, South-East part of Asia



The parasite of malaria is sensitive to the oxidative stress and is killed by a level of stress tolerable by G6PDH deficient human host

→ the deficiency protects agains malaria.

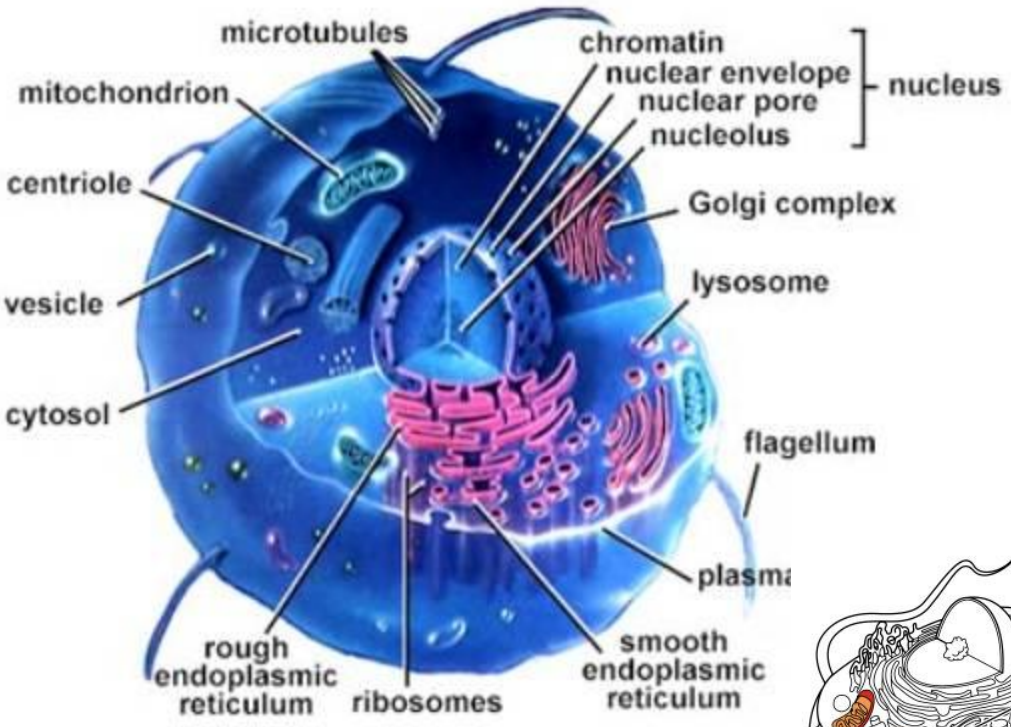

γ-Glu
Cys
Gly
NH3+
CH2
CH2
N
H
CH2
SH

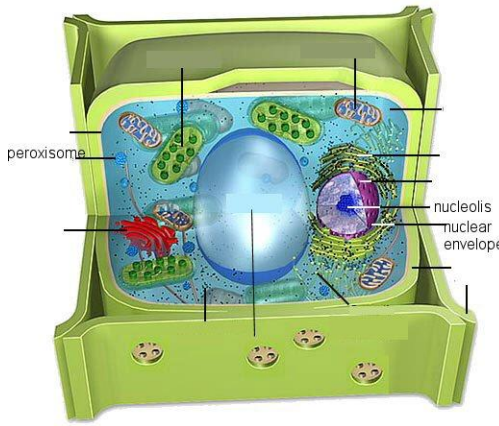

γ-Glu
Cys
Gly
S
S
γ-Glu
Cys
Gly

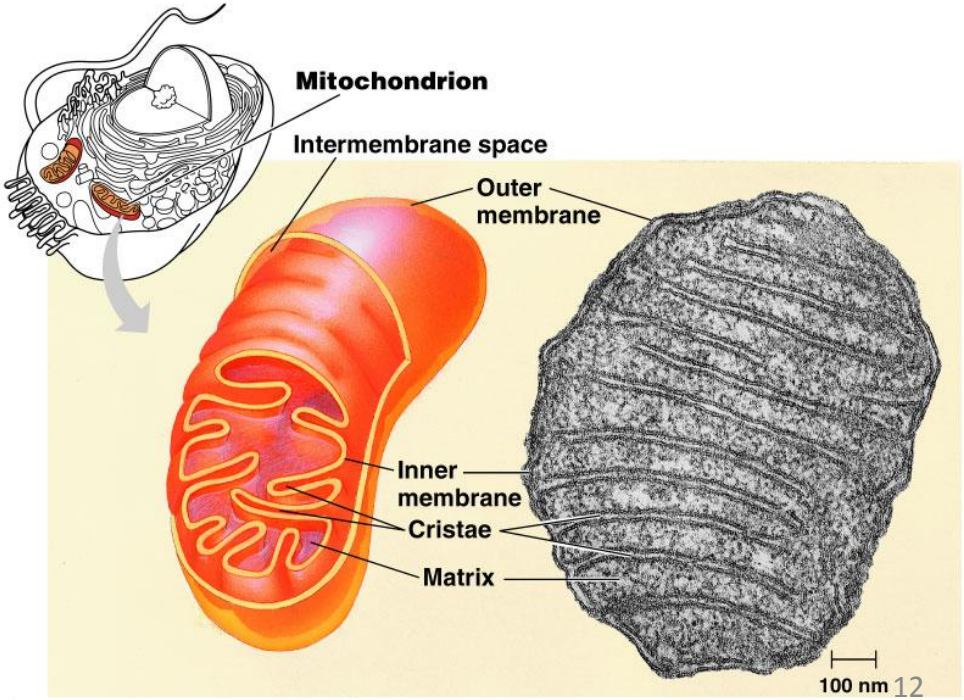
Energy production by cells

1. The conversion of pyruvate to AcCoA (oxidative decarboxilation).
2. The break down of AcCoA to CO_2 and to reduced cofactors (electron carriers) (TCA cycle).
3. The oxidation of reduced coenzimes (electron carriers), the generation of water and energy carrier (ATP).

The mitochondrion







Pyruvate Dehydrogenase Complex

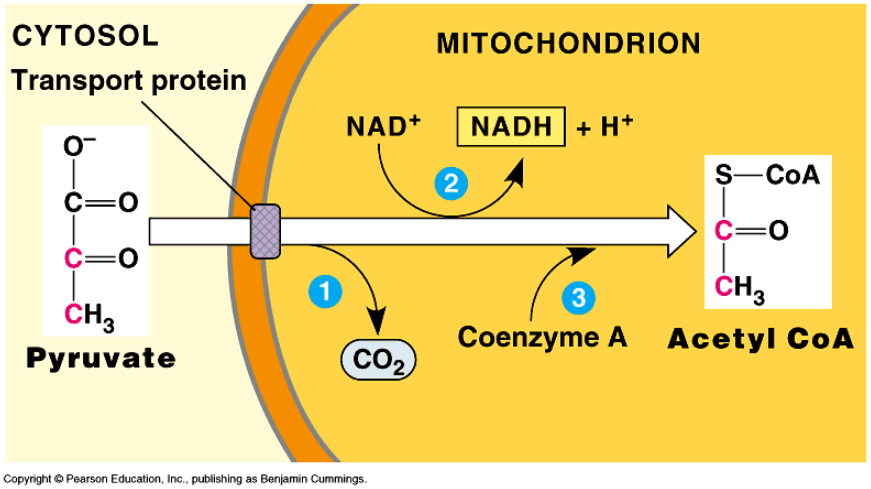
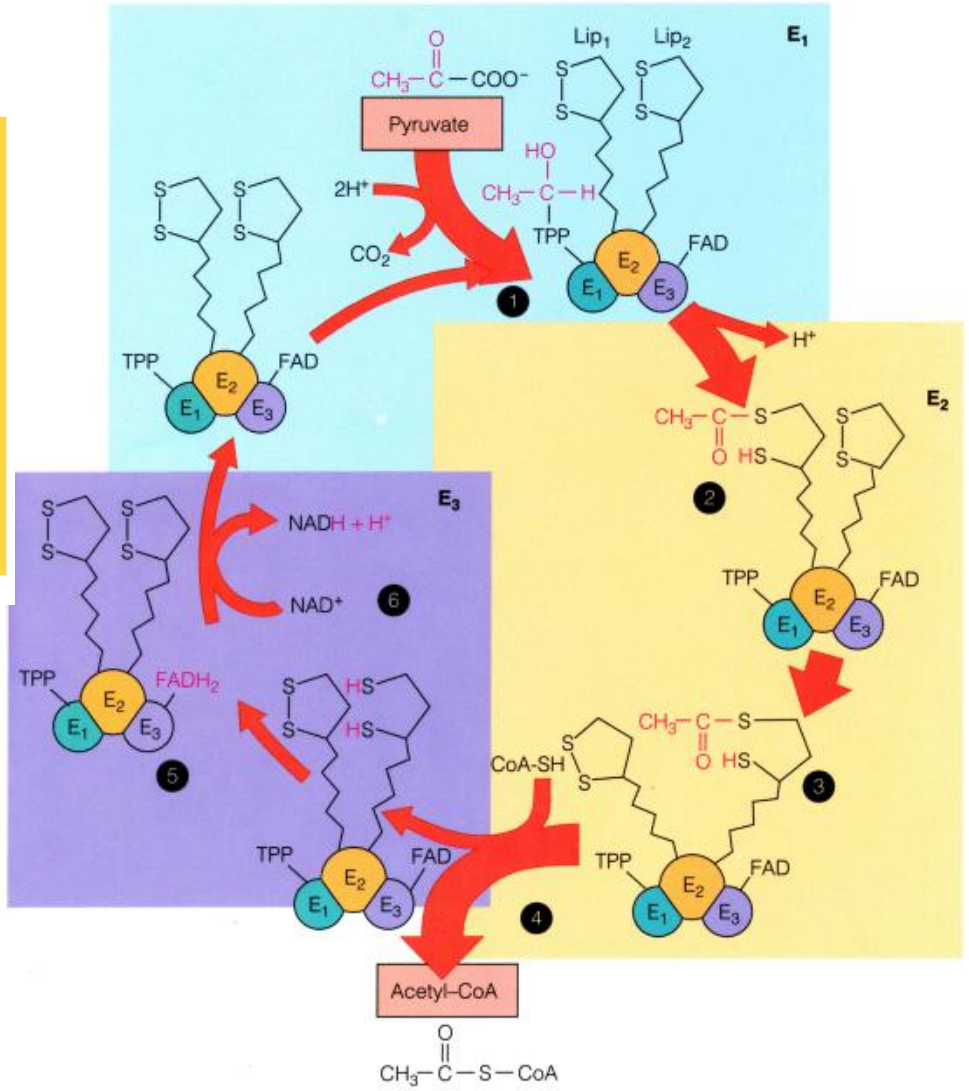


Figure 14.10 Mechanisms of the pyruvate dehydrogenase complex



Pyruvate + CoA + NAD^+ → AcCoA + NADH + H^+ + CO_2

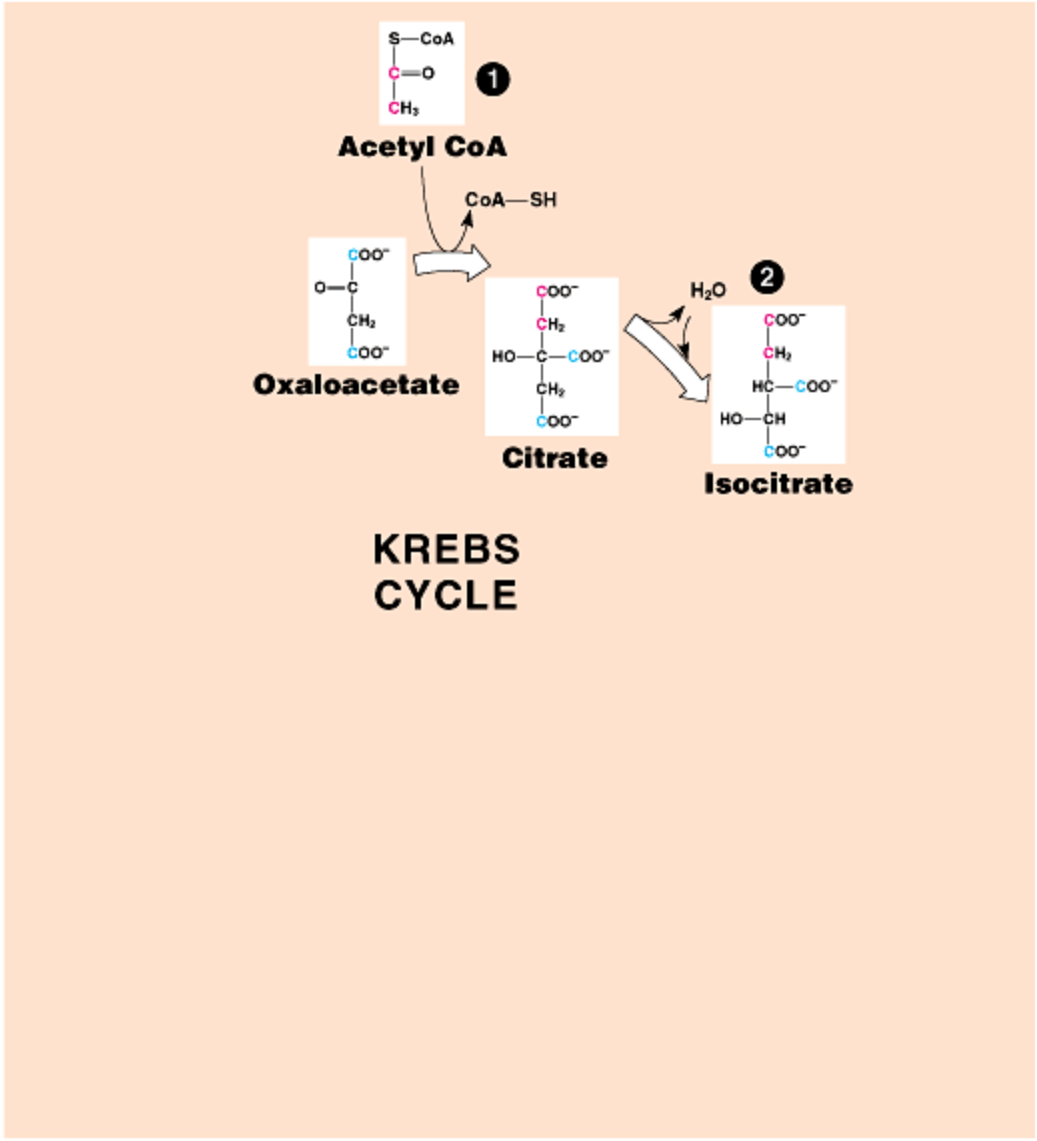
E_1: pyruvate dehydrogenase

E_2: dihydrolypoil-transacetylase

E_3: dihydrolypoil-dehidrogenase

The citrate cycle

(Szent-Györgyi-Krebs cycle, Krebs cycle)



1. **Citrate synthesis**:

Irreversible reaction

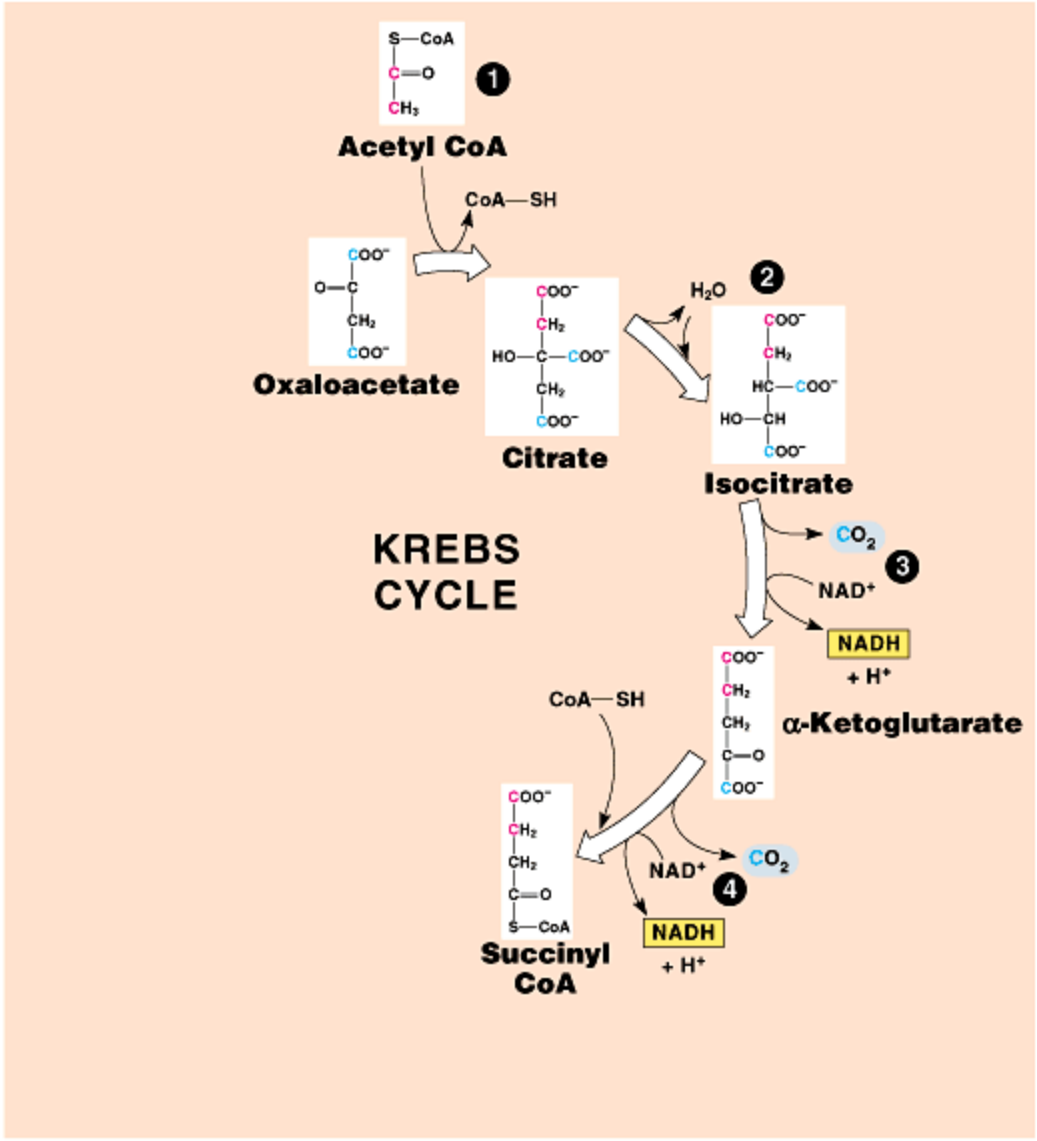
Enzyme: citrate synthase

2. **Isomerisation to isocitrate**

Reversible reaction

Enzyme: aconitase

3. **Isocitrate → α-ketoglutarate**



Irreversible oxidative decarboxilation. Enzyme: isocitrate-dehydrogenase

4. **α-ketoglutarate → succinyl-CoA**

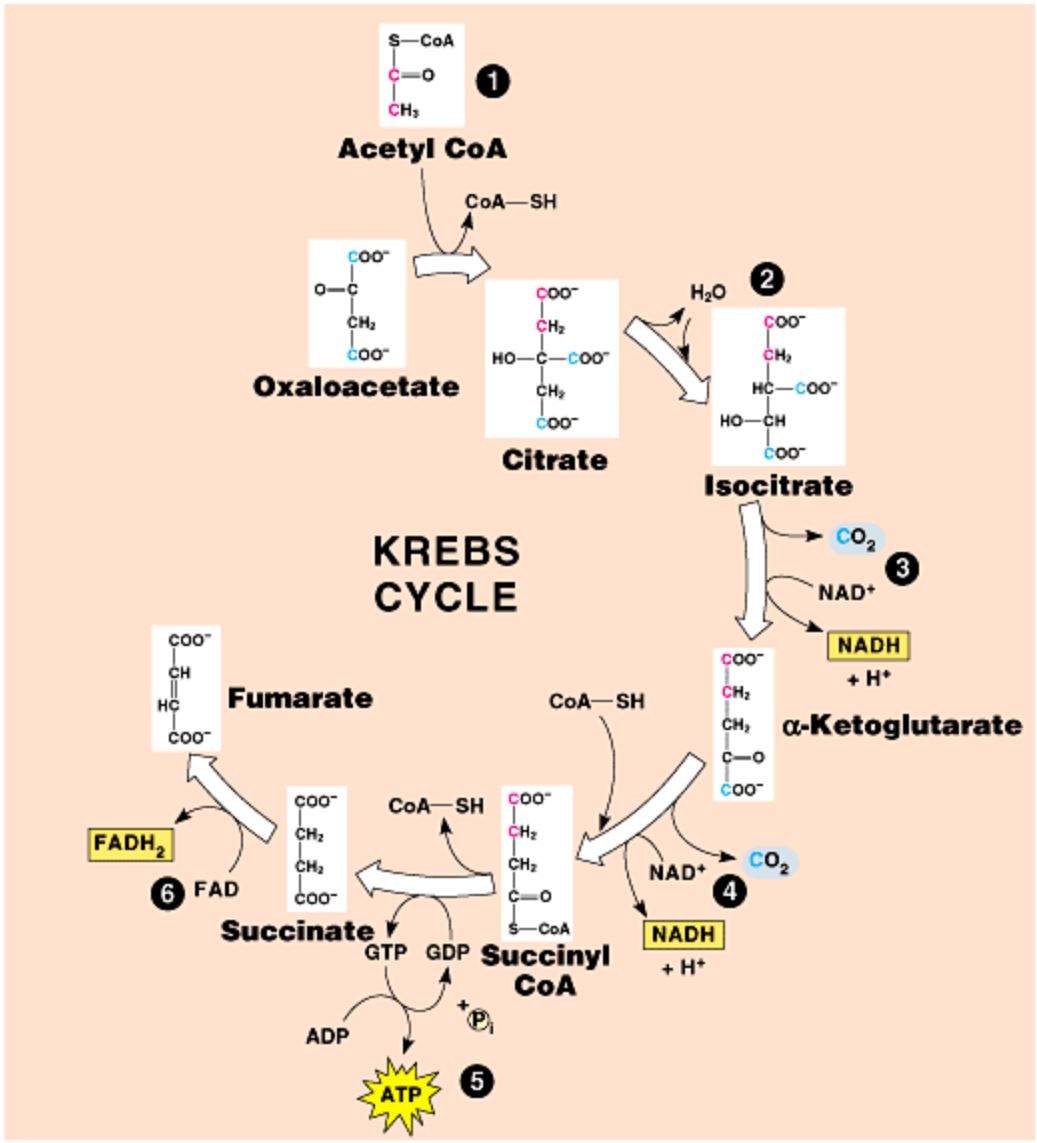
Irreversible oxidative decarboxilation. Enzyme complex: α-ketoglutarate-dehydrogenase

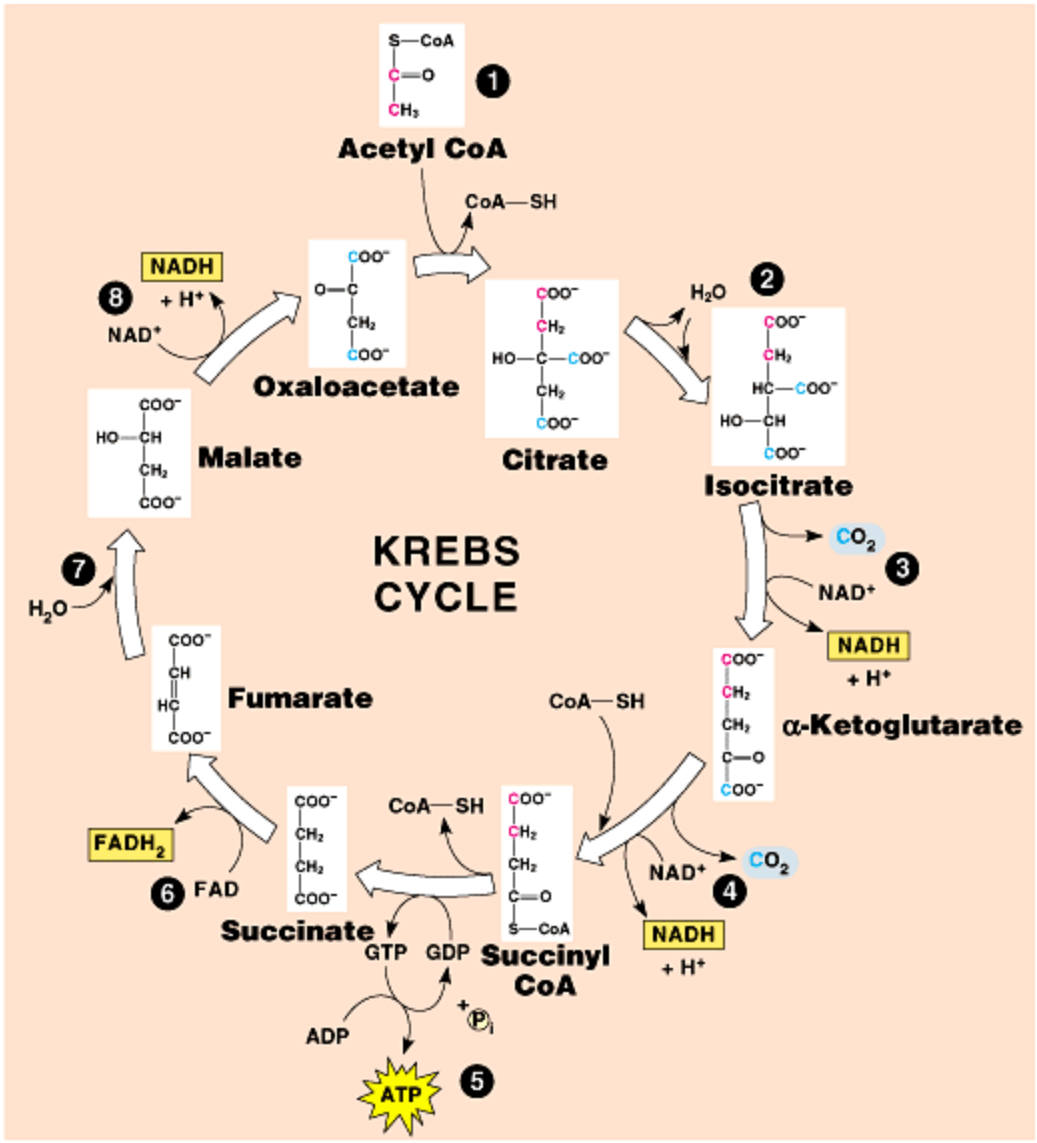
5. Succinyl-CoA → Succinate

Reversible, enzyme: succinyl-CoA synthetase, **substrate-level phosphorylation**

6. Succinate → Fumarate

Reversible oxidoreduction enzyme: succinate dehydrogenase, stereospecific





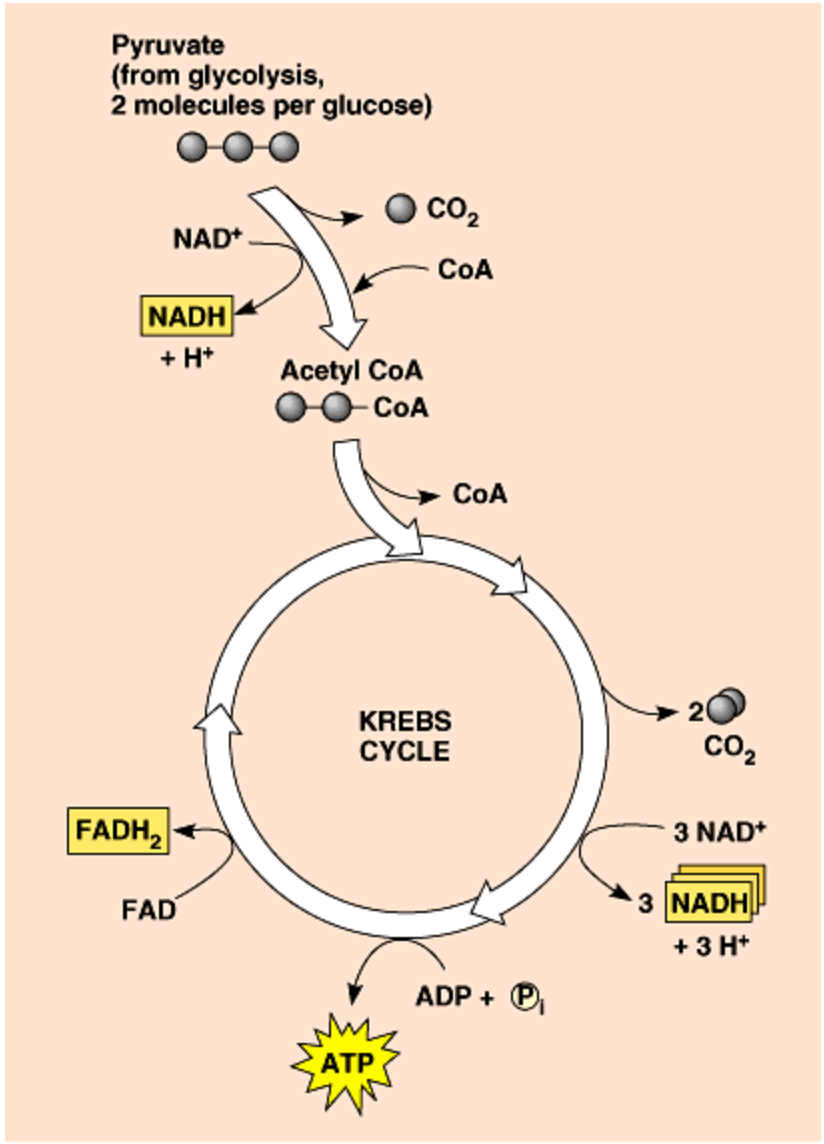
7. **Fumarate → L-malate**

Reversible, stereospecific enzyme: fumarase

8. **Malate → oxalacetate**

Reversible, enzyme: malate-dehydrogenase

The equilibrium constant of the malate dehydrogenase reaction favors the accumulation of malate over oxaloacetate, resulting in a low oxaloacetate concentration



The regulation of TCA cycle

The irreversible steps are regulated

1. citrate synthase
2. isocitrate-dehydrogenase
3. α-ketoglutarate-dehydrogenase

Regulating factors

- NAD/NADH
- ATP/ADP ratio

Anaplerotic reactions, replenish TCA cyce intermadiates

Piruvate + HCO_3^- + ATP ⟷ oxalacetate + ADP + P_i

liver, kidney (gluconeogenesis)

Enzyme: pyruvate carboxylase

Phosphoenol-pyruvate + CO_2 + GDP ⟷ oxalacetate + GTP

heart, skeletal muscle

Enzyme: phosphoenol-pyruvate carboxykinase

Pyruvate + HCO_3^- + NAD(P)H ⟷ malate + $NAD(P)^+$

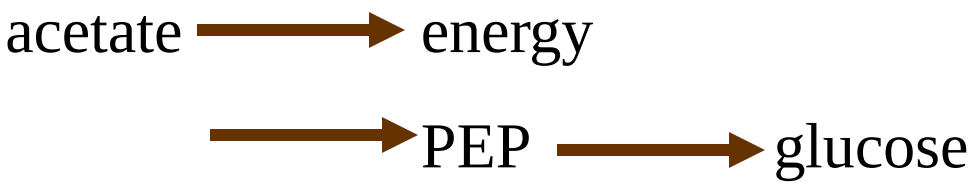
Enzyme: malate enzyme

Glutamate + $NAD(P)^+$ ⟷ α-ketoglutarate + NAD(P)H + H^+ + NH_4

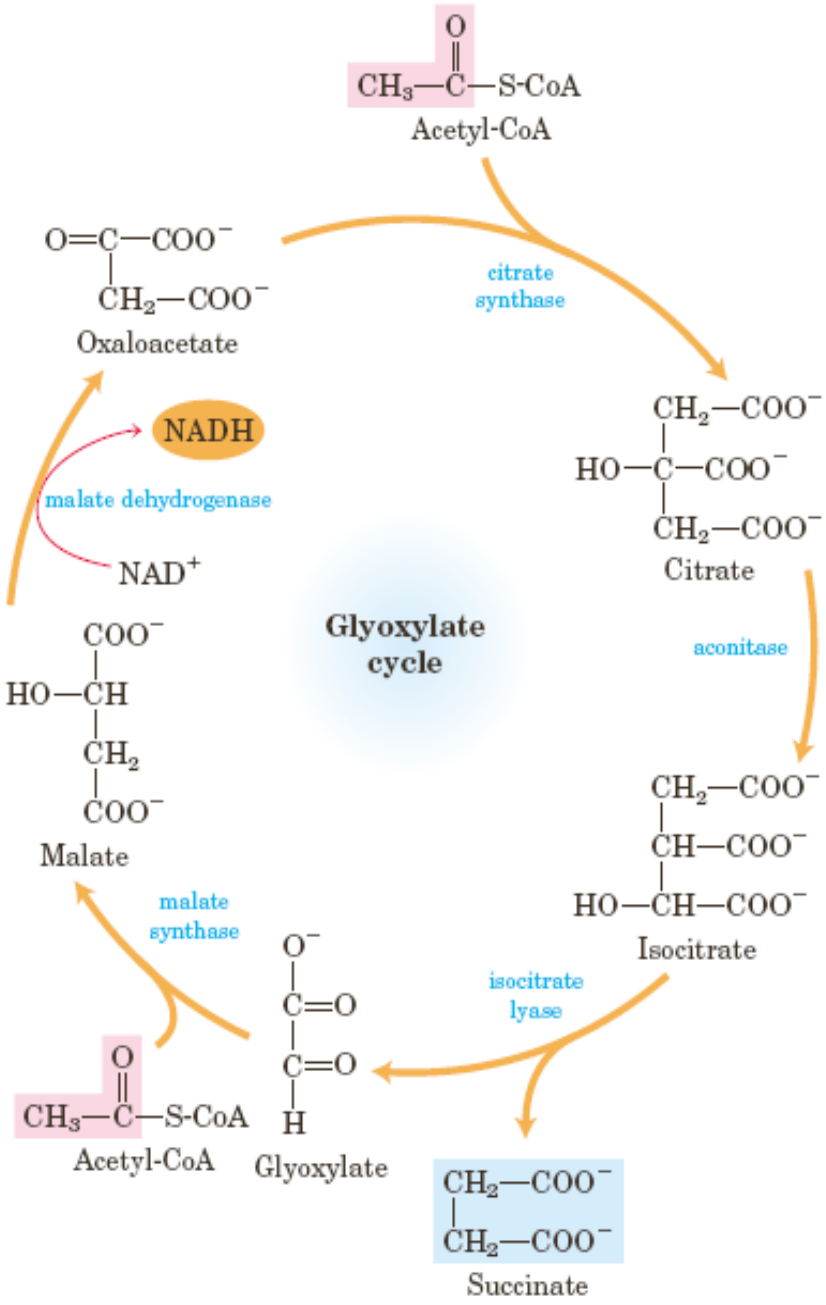
Enzyme: glutamate-dehydrogenase

Vertebrates are not able to synthesize glucose from fatty acids and Ac-CoA

Plants, non vertebrates, microorganisms:



Glyoxalate cycle


Acetyl-CoA
citrate synthase
Oxaloacetate
Citrate
aconitase
Isocitrate
isocitrate lyase
Succinate
Glyoxylate
malate synthase
Acetyl-CoA
Malate
malate dehydrogenase
NADH
NAD+
Glyoxylate cycle